Review Article

Oral Dispersible Tablets: Novel Technology and Development

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ABSTRACT

The review relates to advancements in development of orodispersible tablet formulation to present an impact on drug candidate's characteristics for improvement in bioavailability. The purpose of the article is to review potential advancements of ODT technology in drug delivery applications**.** Various techniques employed to prepare ODTs include direct compression method, freeze drying, spray drying, tablet moulding, sublimation and mass extrusion. ODTs could be preferred choice especially with those drugs sensitive to GI and for patients under category of paediatrics, geriatrics, bedridden, postoperative and who may have difficulty in swallowing the conventional tablets and capsules. Orally disintegrating tablet (ODTs) are solid dosage form that involves the rapid disintegration and dissolution of dosage form presenting as solution or suspension state when placed in the mouth. ODTs render enhanced acceptability due to its patient compliance as well as improved bioavailability and stability. This article reviews recent trends undertaken to develop ODTs, new ODTs technologies, suitability of drug candidate and characterisation of ODTs**.**

Keywords: Solid orals, orodispersible tablet, ODT technology, characterisation.

INTRODUCTION

Most of the pharmaceutical dosage forms are formulated for oral administration where, direct ingestion is intended. In such cases like those with conventional dosage forms, chewing imposes issue in paediatric and the geriatric patients form in. Further psychiatric patients, hospitalised or bedridden patients with chronic diseases finds difficult to swallow solid oral dosage. It is expected that ODTs can address such critical issues. ODTs are solid dosage form that provides the rapid disintegration or dissolution of solid to present as solution or suspension form even when placed in the mouth under limited bio-fluid[1-5.] These Orally disintegrating tablets have various synonyms such as oro-dispersible tablets, quick disintegrating tablets, and mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapimelts. The excipients which are used in ODT technology are usually hydrophilic in nature that could be selected on the basis of drug's physicochemical properties, especially, hydrophillicity or hydrophobicity. If the drug is hydrophobic then dosage form is termed disintegrating tablets whereas, if the drug is hydrophilic then it is called fast dissolving tablets [6]**.** The advantages of this novel solid dosage form are widely recognized, since the term ''oro-dispersible tablet" appears in the European Pharmacopoeia defined as ''uncovered tablet for buccal cavity, where it disperses before ingestion". According to European Pharmacopoeia the ODT should disperse or disintegrate in less than three minutes[7]**.** US FDA defines ODT as a "A solid dosage form containing medicinal substance, which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue" The basic approach in the development in ODT is the judicial use of super disintegrants in the respective formulation composition. Few illustrations include such as cross carmellose sodium, cross povidone, sodium starch glycolate, poly vinyl pyrollidone (PVP) etc. which, produces a fast and spontaneous de-aggregation in the mouth, soon after the contact with saliva. The selection of disintegrating agents depends primarily upon its physical characteristics that render it critical attributes. The active agent can thus rapidly dissolve in the saliva and be absorbed through whatever membrane it encounters, during deglutition, unless it is protected from pre-gastric absorption[4, 8-9]**.** To fulfil these requirements tablets must be highly porous, incorporating hydrophilic excipients, able to rapidly imbibe water for a rapid disaggregation of the matrix. Different techniques, such as freeze drying, spray drying, sublimation, mass extrusion, moulding or direct compression are currently employed to prepare the formulations of this type present on the pharmaceutical market[4, 10-12]**.** The present review is aimed to study recent developments ODT technology, suitability of drug candidate and characterisation of ODTs.

IDEAL PROPERTIES OF ODTS

ODTs are being preferred as advanced dosage form in most instances over conventional immediate release dosage form for various categories of drugs. It is expected to bear certain remarkable features that make them ideal.

For instance ODT disintegrate or dissolves in mouth within a very short time. Further, they do not require water on administration, present acceptable taste masking properties, should have high drug loading capacity, pleasing mouth feel, stable in environmental condition and must not leave any residue in mouth after oral administration[13.]

Due to their rapid presentation of drug at the buccal cavity ODTs would be always dosage form of choice in

case of drugs that are unsuitable to be delivered through GI for many reasons. The advantages offered by ODTs over immediate release formulations may include ease of formulation designing and manufacturing, unit packaging, easy to handle by patients[2, 10, 14-15.], no need of water to administer, rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action that may lead to enhanced therapeutic efficiency due to increased bioavailability [16]. Further, ODT offers ease of administer in paediatric, geriatric, and institutionalized patients (especially for mentally retarded and psychiatric patients) [17-19]. Also, pregastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increase the bioavailability[20].

LIMITATIONS OF ODTS:[21]

- Most of times soluble diluents used for formulating ODTs might render hygroscopic dosage which may lead to stability issues.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
- Specialized packing might be required for hygroscopic and light sensitive drugs.
- Precautions to be taken while administering immediately after removing from pack.
- Light sensitive drugs, ODTs may not be suitable as no option for film coating.

ODT DRUG RELEASE TECHNOLOGY

ODT technology works with aid of superdisintegrants predominant action through interaction with available medium. The mechanistic approach of superdisintegrant in ODTs commence *via* sort of wicking actions that follow steps as given:

Deformation: During tablet compression, disintegrated particles may get deformed but regain their normal shape when they come in contact with aqueous media or water. So this disintegrant particle swell to precompresssion size and produces a breakup of the tablet.[22]

Swelling: Swelling of disintegrates may cause the breaking of tablets[6].

Porosity and capillary action (wicking): When tablets come in contact with aqueous medium, due to penetration of water there may be weakening of bonding force between drug particles. Finally tablet breaks in to fine particles.[6]

Various excipients that are used as a superdisintegrants are mention in table 1.[22-23.]

Table 1: Superdisintegrants

Superdisintegrant	Example	Mechanism of action	Special comment
Crosscarmellose sodium	Crosslinked cellulose	Swells 4-8 folds in < 10 seconds. Swelling and wicking action	Swells in two dimensions. Direct compression. Starch free.
Crosspovidone	Cross linked PVP	Swells very little and return to original size after compression but act by capillary action. Both swelling and wicking action	Water insoluble and spongy in nature so get porous tablet
Sodiumstarch glycolate	Cross linked starch	Swells 7-12 folds in < 30 seconds. Swelling action.	Swells in three dimension.
Alginic acid NF	Cross linked alginic acid	Rapid swelling in aqueous medium. Wicking action.	Promote disintegration in both dry and wet granulation.

ODTs FORMULATION DEVELOPMENT

Various techniques are used in preparation of ODT such as direct compression, sublimation, mass extrusion, moulding, spray drying, and freeze drying. Direct compression is the easiest and most commonly used method for preparing ODT. Conventional equipments, commonly available excipients and limited number of steps are required in direct compression method[7, 13]. Commonly used excipients are diluents, effervescent agents, lubricants, and superdisintegrants. The commonly superdisintegrants used are cross carmellose sodium, cross povidone, sodium starch glycolate, microcrystalline cellulose etc. They aid in rapid disintegration of tablet [24]. The low manufacturing cost is the greatest advantage of direct compression method especially at large scale production levels.

Sublimation Technique: involves, the drug, volatilizing agent and other excipients that are compressed to form a tablet. The volatile material are is then removed by sublimation, which, forms porous structure in tablet. The volatilizing agents are used such as ammonium bicarbonate, camphor, urea, ammonium carbonate [25-26.]

Freeze-Drying: is another technique in which water is removed by sublimation process from the product. This method is used for drying heat sensitive drugs. The tablet formed by this method is highly porous due to which it dissolves rapidly and shows better absorption and bioavailability [7, 24.] The tablet formed by this process is fragile hence it requires a special packing. The major advantage of using this technique is that the tablets produced by this technology have a very low

disintegration time and have great mouth feel due to fast melting effect.

The disadvantage of this technique is expensive and time consuming.

Moulding: In this process the drug is moistened, dissolved or dispersed with the help of hydro-alcoholic solvent and then moulding the moist mixture into tablets, then evaporating the solvent from drug solution by air drying. Moulding process is usually employed with soluble ingredients (saccharides) which, improved mouth feel and disintegration of tablets[26, 27.]

Advantage: It enhances the dissolution rate.

Disadvantage: The moulded tablets have poor mechanical strength, they may undergo erosion and breaking during handling.

Mass Extrusion: This involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste[28.]

Spray Drying: It involves spray drying of blend containing drug, effervescent agent, bulking agent and disintegrating agents which results in production of porous powder. Finally this porous powder is compressed in to tablet[6.]

Cotton Candy Process: cotton candy process involves formation of matrix of saccharides and polysaccharides by simultaneous action of flesh melting and spinning. The matrix formed is partially recrystallized to have improper flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and compressed to ODT. Large drug dosage can be incorporated by this method. This method also offers improved mechanical strength. This process is so named as it utilizes unique spinning mechanism to produce floss like crystalline structure, which mimic cotton candy[29.]

DRUG'S SUITABILITY FOR INCORPORATION IN ODTs[30.]

Some of example of drugs incorporated into ODTs were listed in Table 2.

Other category include Antihypertensive, Ant gout agent, Ant thyroid, Ant migraine, Ant malarial, opoid analgesic, local anaesthetic, stimulant, Neuromuscular agents, gastrointestinal agent also incorporated in ODT's.

There are no particular limitations on the amount of these drugs to be mixed as long as it is the usual effective treatment amount. It should be around 50 weight/weight % or below of the entire tablet, and is preferably 20 weight/weight % or below.

Optimal disintegration properties often have medium to small size and /or high friability and low hardness. Breakage of tablet edges during handling and tablet rupture during the opening of blister alveolus, all result from insufficient physical resistance.

Table 2: List of drugs incorporated into ODTs

Category	Drugs
Analgesics and Anti-inflammatory Agents	Aloxiprin, Auranofin, Azapropazone, Benorylate, Diflunisal,Etodolac, Fenbufen, Ibuprofen, Indomethacin, Ketoprofen, Meclofenamic Acid, etc.
Anthelmintics	Albendazole, BepheniumHydroxynaphthoate, Cambendazole, Thiabendazole etc.
Anti-bacterial Agents	Benethamine Penicillin, Cinoxacin, Ciprofloxacin, Clarithromycin, Doxycycline, Erythromycin, etc.
Anti-Epileptics	Beclamide, Carbamazepine, Clonazepam, Ethotoin, Methoin, Sulthiame, Valproic Acid, etc.
Anti-Arrhythmic Agent	Amiodarone, Disopyramide, Dicoumarol, Phenindione Sulphacetamide, Sulphadiazine, Sulphafurazole, Sulphamethoxazole, Sulphapyridine, Tetracycline, TrimethoprimAcetate, Quinidine Sulphate etc.
Anti-coagulants	Dicoumarol, Dipyridamole Nicoumalone, Phenindione
Anti-Fungal Agents	Amphotericin, Butoconazole Nitrate, Clotrimazole, Econazole Nitrate, Fluconazole, Fiucytosine, Griseofulvin, Itraconazole, Ketoconazole, Miconazole, Natamycin, Nystatin, Sulconazole Nitrate, Terbinafine, Terconazole, Tioconazole, Undecenoic Acid

CHALLANGES IN THE PRODUCT DESIGN, FORMULATION AND MANUFACTURE OF ODTs

Palatability: As most of the drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste masked form. Delivery systems disintegrate or dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence taste masking of drugs become critical to patient compliance[17, 31.]

Mechanical strength: In order to allow ODTs to disintegrate in the oral cavity, they are made of either very porous and soft-moulded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may add to the cost. Only few technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multidose bottles, such as Wowtab® by Yamanouchi-Shaklee, and Durasolv® by CIMA labs[1, 32- 33.]

Amount of drug: Application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. In case of Lyophilized dosage forms, drug dose must be less than 400mg – insoluble drugs less than 60mg -- soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films[1, 17, 31-34.]

Hygroscopicity: Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging[2.]

Size of tablet: The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm. While the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve[35.]

Aqueous solubility: Water soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing point depression and the formation of a glassy solid that may collapse upon drying because loss of supporting structure during the sublimation process. This collapse can be prevented by using various matrix-forming excipients like Mannitol which induces crystallinity and hence impart rigidity to the amorphous composite[10, 36.]

ADVANCEMENTS IN ODT TECHNOLOGIES [37-38.]

Patented and recent advancements in ODT technology are listed in table 3.

Table 3: Patented and recent advancements in ODT technology

Patented technology	Novelty	Handling / storage of dosage form	Drug release
ZYDIS (R.P. SCHERER, INC.)	First to market, a unique freeze-dried tablet with the active drug in a water-soluble matrix, which is then transformed into blister pockets and freeze dried to remove water	Fragility and poor stability during storage under stressful conditions, Packaged in blister packs however a secondary moisture proof foil punch is often required as this dosage form is very moisture sensitive.	Dissolves in 2-10 sec, may allow for pre-gastric absorption leading to enhanced bioavailability
ORASOLV (CIMA LABS, INC.)	Unique taste masking, Effervescent disintegrant used, Lightly compressed.	Soft and fragile tablets, so needed to be packed in specially designed pick and place package system	Disintegrates in 5-45 sec depending upon the size of the tablet, No significant change in drug bioavailability.
DURASOLV (CIMA LABS, INC.)	Similar to Orasolv, but with better mechanical strength	Packaged in blisters or foil or bottles mechanical strength.	Disintegrates in 5-45 sec, No significant change in drug bioavailability.
WOWTAB (YAMANOUCHI PHARMA TECHNOLOGIES, INC.)	Compression moulded tablets, Proprietary taste masking	Avoid exposure to moisture or humidity, packed into bottles and blister packs.	Disintegrates in 15 sec or less depending upon the size of the tablet, No significant change in drug bioavailability.
FLASHDOSE (FUISZ TECHNOLOGIES, LTD.)	Unique spinning mechanism producing floss-like crystalline structure as cotton candy	Avoid exposure to Moisture and humidity, Require specialized Packaging	Dissolves within 1 min., Enhanced bioavailability
FLASHTAB (PROGRAPHARM GROUP)	Compressed dosage form, with drug as microcrystal.	Only conventional tableting technology is required.	Dissolves within 1 min.

Table 4: Advantages and Disadvantages of Patented Technologies[39.]

ZYDIS	Quick dissolution, self preserving, increased bioavailability	Expensive process, poor stability at higher temperature and humidity's.
ORASOLV	Taste masking is twofold, quick dissolution	Low mechanical strength.
DURASOLV	Higher mechanical strength than Orasolv, good rigidity	Inappropriate with larger doses.
WOWTAB	Adequate dissolution rate and hardness.	No significant change in bioavailability.
FLASHDOSE	High surface area for dissolution	High temperature required to melt the matrix can limit the use of heat sensitive drugs, sensitive to moisture and humidity.
FLASHTAB	Only conventional table ting technology is required.	-

CHARACTERISATION OF ODT's[40]

Precompression Parameters

Prior to compression into tablets, the blend is evaluated for properties all essential in-process parameters that are part of intermediate specifications in any development cycle same as conventional IR tablets. However, in case of ODTs these are very critical and important; especially parameters such related to precompression blend micromeritics, which can be part of defining in process quality attributes of the product.

Bulk density (db): Bulk density was determined by weight of powder / volume of powder before tapping.

Tapped density (dt): Tapped density was determined by weight of powder / volume of powder after tapping.

Carr's index/ compressibility index: It indicates powder flow properties and is expressed in percentage. The Carr's index of the powder mix was determined by using formula:

$$I = Dt - Db/Dt * 100$$

Where Dt is tapped density and Db is bulk density.

Carr's index values:[41] CI defines the flow characteristics to the ready for compression blend and thus becomes a very critical in process quality attribute. Usually CI values up to 23 units are acceptable and even stringent 12-18 would be opted for production of low dose highly potent drug in products.

Other parameters defining flow are also evaluated including Hausner ratio, angle of repose,

Hausner ratio parameter that signs indirect index of ease of powder flow. It is calculated taking Hausner ratio= Dt /Db, where Dt and Db are tapped density and bulk density respectively. Alternatively angle of repose can also be calculated to determine the flow properties of the precompression blend. The acceptable range is within 40 units and below 25 units with excellent flow.

Post Compression Parameters [42, 43]

Weight variation: Twenty tablets are selected randomly from the lot and average was checked. Then individual tablets were weight and compare with average weight. None of tablets deviated from average weight by more than ± 5%.

%Weight variation= [(Average weight – Individual weight) / Average weight]*100

Thickness: Thickness of tablets was important for uniformity of tablet size. Thickness was measured using venire callipers on three randomly selected samples**.**

***In vitro* dispersion time:** Tablet was added to 10 ml of phosphate buffer solution pH 6.8 which correlates pH of saliva at 37±0.5ºC and time required for complete dispersion of tablet was noted**.**

Hardness: The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation was determined by Monsanto hardness tester[44.]

Friability test: Twenty tablets were weight and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 min. After revolution the tablets were dusted and weighed. The friability is given by the formula:

$$F = (1- WO/W) \times 100$$

Where, WO is the weight of the tablets before the test and W is the weight of the tablet after the test[45-46.]

Wetting time: The wetting time of the tablets was measured using simple procedure. A piece of tissue papers of 10cm diameter were placed in a petridish containing 6ml phosphate buffer 6.8. A tablet was carefully placed on the surface of the tissue paper. The time for complete wetting was measured. Three trials for each batch and standard deviation was also determined[7.]

Water absorption ratio (r): Water absorption ration can be calculated as

$$R = \frac{\text{Weight of tablet after absorption- Initial weight of tablet}}{\text{Initial weight of tablet}} * 100$$

Dissolution test: The development of dissolution methods for ODT is comparable to approach taken for conventional tablets and is practically identical when ODT does not utilize taste masking. Commonly the drugs may have dissolution conditions as in USP monograph. Other media such as 0.1 N HCl, pH 4.5 and pH 6.8 buffers should be used for evaluation of ODT in the same way as their ordinary tablet counterparts. Experience has indicated that USP 2 paddle apparatus is most suitable and common choice for Dissolution test of ODT tablets, where a paddle speed of 50 rpm is commonly used. Typically the dissolution of ODTs is very fast when using USP monograph conditions. Hence slower paddle speeds may be utilized to obtain a comparative profile. Large tablets approaching or exceeding one gram and containing relatively dense particles may produce a mound in the dissolution vessel, which can be prevented by using higher Paddle speeds. These two situations expand the suitable range of stirring to 25-75 rpm. The USP 1 (basket) apparatus may have certain applications for ODT but is used less frequently due to specific physical properties of tablets [46.]

CONCLUSION

ODTs has increased as it has significant impact on patient compliance and is used to improve the bioavailability and stability. ODTS are alternative for drug delivery to paediatrics and geriatric patients. The basic approach in the formulation of ODTs tablets are to increase porosity of tablet and incorporate superdisintegrants in optimum

concentration to achieve rapid disintegration and instantaneous dissolution of tablet along with good taste masking properties and excellent mechanical strength. Thus ODT has tremendous scope for being the delivery system for most of the drugs in near future.

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